

TAB B



United States
CONSUMER **PRODUCT** SAFETY COMMISSION
Washington, D.C. 20207

APR 1 1998

MEMORANDUM

TO: Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for Epidemiology and Health Sciences

THROUGH: Marilyn L. Wind, Ph.D., Director, Division of Health Sciences, *MLW*
Directorate for Epidemiology and Health Sciences

FROM: Jacqueline N. Ferrante, Ph.D., Pharmacologist, Division of Health Sciences, *JF*
Directorate for Epidemiology and Health Sciences

SUBJECT: Sucraid Review

Introduction

Orphan Medical petitioned the Commission to exempt **Sucraid™**, an oral solution of the enzyme sacrosidase, **from** special packaging requirements for oral prescription drugs under the Poison Prevention Packaging Act (PPPA). This memorandum reviews scientific information related to **Sucraid™**.

Product Description and Use

Sucraid™ is the brand name for sacrosidase, a yeast-derived form of the sucrase enzyme. This enzyme is obtained from baker's yeast which is also **known as *Saccharomyces cerevisiae***. **Sucraid™** contains 1.5 milligrams (8,500 International Units) per milliliter (mg/ml) of the enzyme in a **50:50** solution of glycerol and water at an unbuffered slightly acidic pH of 4.6. **Sucraid™** is the only available treatment for congenital sucrase-isomaltase deficiency (CSID). It is replacement therapy for sucrase, not isomaltase. The petitioner argues that the confectionery and baking industry has used this enzyme extensively and that under 21 CFR 170.30 it is a "Generally Recognized as Safe" (GRAS) food material because of its long history of safe use in humans. It is used as a flavoring agent and adjuvant at a level not to exceed five percent in food.

The recommended dose of **Sucraid™** for patients with CSID is one ml per meal or snack for patients weighing up to 15 kilograms (kg) (33 pounds) and 2 ml for patients over 15 kg. The dose should be diluted in 2 to 4 ounces of water, milk, or infant formula. Studies suggest that milk is the liquid of choice for preserving enzyme activity.

Contraindications to the use of **Sucraid™** are in patients with a known hypersensitivity to yeast, yeast products, or glycerol. Additionally, **Sucraid™** should be used with caution in diabetics because the subsequent conversion of absorbed sucrose to glucose and fructose may alter blood glucose levels. The manufacturer recommends refrigeration of **Sucraid™** and that unused portions be discarded four weeks after opening because of the potential for bacterial growth.

Congenital Sucrase-Isomaltase Deficiency (CSID)

CSID is an autosomal recessive disease of the small intestine characterized by low or absent sucrase activity, a marked reduction in isomaltase activity, and a moderate decrease in maltase activity (1, 2). The sucrase-isomaltase complex is one of four brush-border enzymes of the small intestine. It is synthesized as a single polypeptide chain that is eventually cleaved by proteases to form a heterodimer. A precise genetic mutation has not been elucidated in CSID patients, but defects in post-translational events including glycosylation, folding, intracellular transport, and membrane insertion of the enzyme have been documented. CSID can also result secondary to **diffuse** mucosal injury (2).

Treem, 1995 (2) has described the activities of the brush border enzymes. Normally, sucrase hydrolyzes or breaks down the glucose-fructose linkage of sucrose and the α 1-4 linked glucose bonds of maltose (2 glucose molecules) and maltotriose (3 glucose molecules). Isomaltase hydrolyzes the 1-4 bond of maltose, the 1-6 bond of isomaltose and the α 1-6 glucose bonds of α -limit dextrins. The activity of another brush border enzyme, maltase-glucoamylase, overlaps with that of sucrase-isomaltase. **Maltase-glucoamylase** hydrolyzes α 1-4 glucose linkages of maltose, maltotriose, starch, glycogen, and other oligosaccharides. Sucrose-isomaltase accounts for 80% of the maltase activity while maltase-glucoamylase is responsible for only 20%.

Sucrose (table sugar) is a disaccharide derived commercially from sugar cane or sugar beets. Patients with CSID, who lack the endogenous sucrase enzyme, are unable to digest and absorb sucrose and experience symptoms including watery diarrhea, bloating, abdominal pain, and flatulence. Undiagnosed infants with CSID may have severe, protracted diarrhea associated with failure to thrive (3). A small number of severely affected patients require hospitalization for diarrhea, dehydration, malnutrition, muscle wasting, and weakness (2). The diarrhea results from the malabsorbed carbohydrate which acts as an osmotic laxative drawing water and electrolytes into the intestinal lumen (4). Bacterial metabolism of the undigested carbohydrates produce the gas which distends the colon.

Typically, patients with CSID have a stool pH of between 5 and 6 and an increase in breath hydrogen (2). However, direct measurement of enzyme activity from small bowel biopsy samples is the most definitive test. CSID has been diagnosed in some infants when juices, solid foods, or medications sweetened with sucrose are added to their diet. Adults diagnosed with CSID have a history of eating difficulties and intermittent symptoms from infancy and the enzyme deficiency may be uncovered by an enteric infection (2).

CSID is rare in most populations, but the prevalence may be underestimated because some patients are undiagnosed (2). The prevalence of CSID is 0.2% in North Americans and higher in Eskimos from Greenland (2 - 10 %), Alaska (3%), and Canada (~ 4 - 7 %) (1, 2, 5). The petitioner estimates that there are approximately 3,000 to 10,000 cases in the U.S.

Treatment of CSID

Elimination of sucrose from the diet is one treatment option for patients with CSID. However, maintaining a sucrose-free diet is difficult (1). Another alternative is to replace the enzyme in the diet. This was initially tried using baker's yeast which naturally contains sucrase. An 11-year-old female with CSID prevented symptoms of diarrhea and abdominal pain by adding fresh baker's yeast to her sucrose-containing diet. Based on this result, enzyme substitution therapy with lyophilized baker's yeast was studied in eight children with CSID (5). A dose of 0.3 grams (g) administered after a loading dose of 2 g/kg of sucrose

*Measurement of breath hydrogen is one diagnostic test for CSID. In most subjects, colonic flora produce hydrogen from malabsorbed carbohydrates. Therefore, breath hydrogen is usually elevated in CSID patients (> 10 parts per million over the baseline level) (2, 4).

reduced or eliminated symptoms associated with CSID (i.e., bloating, cramps, and diarrhea) and lowered breath hydrogen. No adverse effects were described from this treatment.

Enzyme replacement therapy with **Sucraid™** is a more palatable alternative to baker's yeast (1). It may be easier to administer to young children because it is diluted before use in drinks normally consumed by children (i.e., milk, water, and formula).

Experimental Data

Animal Studies

Animal testing was not required to assess the toxicity of **Sucraid™** because of the availability of the yeast-derived enzyme as a food grade product. Orphan Medical requested a waiver of nonclinical pharmacology tests **from** the FDA based on: 1) the nature of the enzyme as a replacement for a missing endogenous one; 2) a clear demonstration of the efficacy of the enzyme in humans; and 3) the unavailability of appropriate animal models for CSID. According to the petitioner, pharmacokinetic (absorption, distribution, metabolism, and excretion) and LD50² studies of **Sucraid™** were not performed based on its lack of toxicity, the extensive database of use in humans, and its long-term use in the baking and confectionery industry.

Human Clinical Trials

The petitioner submitted human experience data to support the exemption request. According to the petitioner, there have been three clinical trials of **Sucraid™**. Two of three are complete. Clinical investigators conducting these trials determined that none of the reported adverse effects were probably or definitely related to **Sucraid™**. The majority of adverse events were described as either symptoms of a concurrent illness **common** in children (e.g., flu, upper respiratory infection, or otitis media) or GI symptoms routinely associated with CSID (e.g., diarrhea, nausea, vomiting, or abdominal pain).

The objective of the first trial (Study S-1) was to determine the effect of **Sucraid™** on GI symptoms and breath hydrogen excretion after a large sucrose ingestion, and to establish a dosage range of **Sucraid™** for a normal sucrose-containing diet. This study was published in the medical literature (1) and involved 14 CSID patients with a mean age of 7.6 years (range, 0.7 - 29 years). For the two randomized breath hydrogen tests, patients ingested sucrose followed by placebo or **Sucraid™**. GI symptoms were documented during and eight hours after each test. For the dose-response study, patients were given each of four dilutions of **Sucraid™** (1: 100, 1: 1000, 1: 10,000, and 1: 100,000) in random order for 14 days each. GI symptoms **and** stool frequency and consistency were documented daily. The results of the study showed that **Sucraid™** reduced breath hydrogen excretion in CSID patients given sucrose and GI symptoms (diarrhea, abdominal pain, and gas) were reduced or prevented.

²Median lethal dose.

Most patients ingesting 1 ml of the 1 :100 dilution of the enzyme with each meal experienced minimal symptoms, whereas symptoms of diarrhea, abdominal pain, and excessive gas were more prevalent with increasing dilution of the enzyme indicating that the underlying disease, not the drug, was responsible for the symptoms (1).

Eight of 14 patients had at least one adverse event including fever, flu, headache, vomiting, congestion, side pain, runny stools, rectal bleeding, and ear problems. A total of 17 adverse events **were** reported, eight were considered by the investigator to be related to a concurrent illness and nine were rated as unknown or unrelated to the drug. No adverse events were rated as possibly or probably drug related. There were no serious adverse events or withdrawals due to adverse events during the trial. Four patients withdrew **from** trial S-1 after treatment. These patients were lost to follow-up.

The second trial (S-2) tested Sucraid™'s ability to prevent or reduce breath hydrogen excretion in CSID patients **after** a large dose of sucrose and to prevent GI symptoms associated with a normal sucrose-containing diet. There were three breath hydrogen tests after a sucrose dose of 2 g/kg followed each by placebo, sacrosidase, or **milk/sacrosidase**. Each test was separated by one week. Patients were instructed to maintain a sucrose-free/low starch diet during the week. In the dose-response phase, patients maintained a normal sucrose-containing diet while receiving each of four concentrations of **Sucraid™** (full-strength enzyme, 1: 10, 1: 100, and 1: 1,000) in random order for 10 days each. Twenty-six of 34 patients experienced at least one adverse event in this trial. Most of the adverse events (49/95, 52%) were attributed to concurrent illnesses and the investigator considered these to be unrelated to the enzyme. Included were 12 patients **who** only experienced symptoms that were unrelated including sore throat, fever, cough, and runny nose. These symptoms were attributed to concurrent illnesses such as viral infection, ear infection, and strep throat. Diarrhea, cramping, and abdominal pain were also observed in some of these patients, but were considered unrelated because they were observed while the subject had the flu, was between the breath hydrogen and dose response study phases, or after the subject was given a placebo. Eleven of 26 had one or more adverse events that the investigator considered possibly related to **Sucraid™**. Symptoms included abdominal pain, diarrhea, nausea, vomiting, constipation, dehydration, cramps, headache, insomnia, nervousness, shock, and wheezing.

The petitioner noted that many of these symptoms are typical of CSID and that most of the patients tolerated the enzyme well enough to complete both phases of the trial. It is possible that a given dose of **Sucraid™** was not **sufficient** enough to alleviate the symptoms of CSID in all of the subjects. There is variation in the expression of symptoms in CSID patients depending on residual endogenous enzyme activity, the rate of gastric emptying, the effect on small bowel transit, the metabolic activity of **colonic** bacteria, and the absorptive capacity of the colon (2).

There were no deaths in trial S-2. Of six patients who withdrew from trial S-2, only one withdrew because of an adverse event. This patient, a **48-month-old** male, started wheezing 90 minutes after receiving a dose (2 ml) of the **full** strength enzyme. He was taken to the emergency room and admitted to the intensive care unit. He was discharged the following day. The child had a history of asthma and was being treated with steroids. This information was not reported to the clinical investigator or trial coordinator prior to the trial. The child was rechallenged with **Sucraid™** and the skin test was positive.

There were three other patients who fit the definition of a serious adverse event in trial **S-2**, **which** was defined as “any event that was fatal or life-threatening, was permanently disabling, required inpatient hospitalization (or an emergency room visit without hospitalization), or was a congenital anomaly, cancer, or overdose.” The patients in these cases required inpatient hospitalization or an emergency room visit. **Sucraid™** was only possibly related to the observed adverse effects in two cases and unrelated in one. Notably, none of these patients suffered any residual disability and all three subjects completed the trial and continued on **Sucraid™** treatment. Patient summaries for these three patients are described below.

► Prior to **Sucraid™** treatment, a 6-month-old female patient had elective surgery for closure of a colostomy between the breath hydrogen and dose-response trials. The patient recovered from surgery, completed the trial, and continued with sacrosidase treatment. The investigator determined that these events were not related to **Sucraid™**.

► An 8-month-old female was treated for otitis media with an antibiotic 13 days after starting **Sucraid™** treatment. The patient started treatment with a 1: 1000 dilution of **Sucraid™** on the same day as the antibiotic. The child vomited immediately following a dose of antibiotic after dinner. Two days later she experienced projectile vomiting, had gray skin, and white lips and was admitted to an emergency room. The severity of these events were not reported. Her color returned after she vomited mucous and symptoms of congestion and red ear were reported. **Sucraid™** treatment was stopped during these events, but re-initiated about 2 1/2 weeks later. The investigator considered the vomiting after the antibiotic unrelated to **Sucraid™**, but the other effects (projectile vomiting, gray skin, and white lips) possibly related to **Sucraid™**. Nevertheless, the patient completed the trial and continued on **open-label³ Sucraid™** with meals and snacks.

. A 47-month-old-male became dehydrated after **Sucraid™** treatment and was admitted to the hospital for rehydration. The discharge date and the outcome were unavailable. The patient also experienced nausea, vomiting, and diarrhea. Treatment was stopped about a month later for an unspecified reason. The child eventually had same-day surgery to remove a benign mass on his right breast. He became dehydrated after discharge and was readmitted to the hospital for rehydration. The outcome was described as “apparently satisfactory.” The patient completed the trial and continued on open-label **Sucraid™** with meals and snacks.

³Open label means that patients are given **Sucraid** who need it. It is not part of the clinical trial.

The investigator considered that only the first episode of dehydration was possibly related to **Sucraid™**. The nausea, vomiting, diarrhea, right breast mass, and second episode of dehydration following surgery were considered unrelated to **Sucraid™**.

Toxicity

The enzyme in **Sucraid™** is a glycoprotein with a known amino acid sequence. It has an apparent molecular weight of 97 kD and is fully soluble with water, milk, and infant formula. One bottle of sucraid (118 ml) contains the equivalent of 150 mg or 0.15 g of protein. This is a small fraction of total dietary protein which is usually about 125 g/day (6). The petitioner reasoned that no direct systemic toxicity from the enzyme in **Sucraid™** is possible because it would not be absorbed intact due to its large molecular size. As with other proteins ingested in the diet, it will be digested in the GI tract to polypeptides and subsequently to its constituent amino acids. Amino acids are used to synthesize new proteins, are burned for energy, or are converted to carbohydrates or fats. Therefore, they would not be expected to cause toxicity. Protein digestion begins in the stomach where the enzyme, pepsin, cleaves bonds involving tyrosine and phenylalanine (6). Proteins are further digested in the small intestine by a number of enzymes including trypsin, chymotrypsin, and various peptidases. Dietary proteins, enzyme proteins secreted into the GI tract by various glands, and protein from sloughed mucosal cells are digested and absorbed in the small intestine (6).

The enzyme in **Sucraid™** is dissolved in a 50:50 solution of glycerol (or glycerin) and water. The petitioner identifies glycerol as the most toxic component of the product. Glycerol is a sweet syrupy liquid valued for its solvent, preservative, and moisturizing properties (7). It is "Generally Recognized as Safe" by the FDA as a food for human consumption (21 CFR 182.1320). Glycerol has many industrial and pharmaceutical uses. These include its use as a sweetening agent, a preservative in liquid medications, a plasticizer in tablet film-coating, a lubricant in eye drops, lotions and creams, and a demulcent in cough preparations (7).

Pharmacologically, glycerol is classified as an osmotic diuretic. These agents are freely filtered at the glomerulus, undergo limited renal tubule reabsorption, and are relatively inert pharmacologically (8). Given orally or parenterally, glycerol increases plasma osmolality leading to the movement of water from extravascular spaces into the plasma (7). It is used to reduce intraocular and intracranial pressure. The usual dose of glycerol for reducing intraocular pressure is 1 to 2 g/kg given as a 50% or 75% solution (7, 9). Additional doses of 0.5 g/kg may be given if required. <Glycerol is also classified as a hyperosmotic laxative and may be given rectally as a suppository or solution in single doses (7).

Glycerol is well absorbed after oral administration and is primarily metabolized in the liver. Peak serum concentrations are reached in 60 to 90 minutes (10). Glycerol may be utilized in lipid synthesis, metabolized to glucose or glycogen, oxidized to carbon dioxide and water, or be excreted unchanged in the urine (7).

Adverse effects associated with glycerol include nausea, vomiting, headache, and dehydration. Less frequently reported effects include diarrhea, thirst, dizziness, and mental confusion. Cardiac arrhythmias have also been reported. **Hemolysis⁴, hemoglobinuria⁵**, and renal damage have been documented with intravenous (IV) administration of glycerol (10). These effects have been observed at doses of 0.5 to 2 g/kg (10). IV glycerol treatment (50 g as a 10% solution in isotonic saline) in 500 patients with elevated intracranial pressure had no deleterious effects when administered over 6 hours for 7 to 10 days. However, hemolysis was observed in 4 of 70 patients when the infusion was given more rapidly over 60 to 90 minutes at a rate of 7 to 14 **mg/kg/min** (10, 11). In another report, IV administration of 1 g/kg glycerol at a higher concentration of 20% to three patients at a rate of 15, 30, and 60 minutes, respectively, resulted in hemolysis in all three patients and renal damage in one patient (12).

The expansion of extracellular fluid caused by glycerol may lead to circulatory overload, pulmonary edema, and congestive heart failure, particularly in high risk patients with cardiac failure, renal or hepatic disease, dehydration, and hypervolemia (7). Diabetics are another risk group because of the dehydrating effects of glycerol and hyperglycemia may develop following its metabolism. Hyperosmolar nonketotic coma is rare, but deaths have been reported (7).

The petitioner calculated that a four ounce bottle of **Sucraid™** contains about 71 grams of glycerol, which is equivalent to a dose of 7.1 g/kg in a 10 kg child. Human toxic or lethal doses of glycerol have not been defined. While effects of a more serious nature have been described following IV glycerol treatment or in high risk patients, the Hazardous Chemicals Desk Reference (13) indicates that glycerol is mildly toxic by ingestion. The petitioner also cited a prescription drug product, Osmoglyn, which is a pre-surgical 50% solution of glycerol used to reduce intraocular pressure (9). The toxicologic management for Osmoglyn in the **Poisindex®** (14) categorizes it as a non-toxic ingestion. According to the **Poisindex®**, “materials referenced to this management have been considered very unlikely to produce any toxicity except in enormous doses.”

Additionally, the **Handbook of Common Poisonings in Children** (15) categorizes glycerol as a laxative and states that “acute exposure to most laxatives produces nausea, vomiting, and diarrhea, which are usually mild and self-limiting.” Significant fluid loss and dehydration are uncommon. Typically, the only treatment required after a single severe exposure to laxatives is observation and fluid replacement, if needed. There were three ingestion cases in children under five years old in the National Electronic Injury Surveillance System (**NEISS**) database that involved products with glycerol. The products ingested were a glycerol suppository, a baby enema preparation, and an ear solution. In all three cases the disposition was defined as treated and released, or examined and released without treatment.

⁴The destruction of red blood cells.

⁵The presence of hemoglobin in the urine.

Conclusion

Sucraid™ is used to treat patients with CSID. The **enzyme** in **Sucraid™** is derived from a yeast, but it is also normally found in humans where it functions to break down sucrose. It is a large glycoprotein that will be digested by GI enzymes to amino acids that will be used as nutrients. Because **Sucraid™** is a new product there is limited information available concerning its toxicity. Medical literature searches by the petitioner and the Commission staff failed to retrieve toxicity information related to the **Sucraid™** enzyme. The only available toxicity information derives from studies conducted by the petitioner who argues that clinical experience with **Sucraid™** in patients 5 months old and greater has not shown evidence of significant toxicity or intolerance.

Fifty-two patients were treated with **Sucraid™** in clinical studies up to a duration of 54 months. In only one case did a patient withdraw because of an adverse event. This involved an asthmatic patient who had an acute hypersensitivity reaction to **Sucraid™** which resolved without sequelae. The number of patients reporting other adverse events that the clinical investigator determined to be possibly related to **Sucraid™** include (4) abdominal pain, (3) vomiting, (2) nausea, (2) diarrhea, (2) constipation, (1) insomnia, (1) headache, (1) nervousness, (1) facial edema, and (1) dehydration. The petitioner asserts that these effects were generally **minor** and frequently associated with CSID. Furthermore, most of the patients tolerated the enzyme well enough to complete the studies.

No cases of intentional or accidental overdose of **Sucraid™** have been reported. Glycerol is another component of **Sucraid™**. Many of the known side effects of oral glycerol are minor and include headache, nausea, vomiting, and dizziness. The more serious adverse effects associated with glycerol are those observed in high risk patients or following IV administration. Moreover, the **Poisindex®** categorizes the management for a prescription product with the same percentage of glycerol as **Sucraid™** as a non-toxic ingestion. The existing data do not show that the handling, use, or ingestion of **Sucraid™** by children would cause them serious personal injury or illness.

•

References

1. Treem, W.R., Ahsan, N., Sullivan, B., **Rossi**, T., Holmes, R., Fitzgerald, J., Proujansky, R. and **Hyams, J.** **Evaluation** of Liquid Yeast-Derived **Sucrase** Enzyme Replacement in Patients with Sucrase-Isomaltase Deficiency. *Gastroenterology* 105: 1061-1068, 1993.
2. Treem, W.R. Congenital Sucrase-Isomaltase Deficiency. *J. Ped. Gastroenterology and Nutrition* 21:1-14, 1995.
3. Newton, T., Murphy, M.S. and Booth, I.W. Glucose Polymer as a Cause of Protracted Diarrhea in Infants with Unsuspected Congenital Sucrase-Isomaltase Deficiency. *J. Pediatr* 128:753-6, 1996.
4. Kemer, J.A. **Formula** Allergy and Intolerance. *Gastroenterology Clinics of North America* 24:1-25, 1995.
5. Harms, H., Bertele-Harms, R. and Bruer-Kleis, D. Enzyme-Substitution Therapy with the Yeast *Saccharomyces Cerevisiae* in Congenital Sucrase-Isomaltase Deficiency. *N. Engl. J. Med.* 316:1306-9, 1987.
6. Human Anatomy and Physiology, Elaine N. Marieb, The **Benjamin/Cummings** Publishing Company, Inc. 1989.
7. Martindale, The Extra Pharmacopoeia, Thirty-first Edition, James E.F. Reynolds, Ed., Royal Pharmaceutical Society, 1996.
8. Goodman & Gilman's The Pharmacological Basis of Therapeutics, "Osmotic Diuretics," pp. 695-696, Joel G. G. **Hardman** & Lee E. Limbird Eds. McGraw-Hill, Ninth Edition, 1996.
9. Facts and Comparisons, Osmotic Diuretics, p.139j, J.B. Lippencott Co., St. Louis, MO., 1995.
10. **Frank, S.B.**, Nahata, M.C. and Hilty, M.D. Glycerol: A Review of its Pharmacology, Pharmacokinetics, Adverse Reactions, and Clinical Use. *Pharmacotherapy* 1: 147-160, 1981.
11. Welch, K.M.A., Meyer, J.S., Okamoto, S., **Mathew**, N.T., **Rivera**, V.M. and Bond, J. Glycerol-induced hemolysis. *Lancet* 1:416-417, 1974.
12. Hagdevik, K., Gordon, E., Lins, L., Wilhelmsson, S. and Forster, D. Glycerol-induced Hemolysis with Hemoglobinuria and Acute Renal Failure. *Lancet* 1:75-77, 1974.
13. Lewis, R.J. Sr., Hazardous Chemicals Desk Reference, Third Edition (Van Nostrand Reinhold, NY.), 1993.

14. **Poisindex®** System. Rumack, B.H., Hess A.J., & **Gelman**, C.R. (Eds). Micromedex, Inc., Englewood, Colorado, 1997.
15. Handbook of Common Poisonings in Children, American Academy of Pediatrics, **Third** Edition, Rodgers, G.C. and Matyunas, N.J. (Eds.), 1994.

TAB C





United States
CONSUMER PRODUCT **SAFETY** COMMISSION
Washington, D.C. 20207

MEMORANDUM

DATE: April 2, 1998

TO : Jacqueline N. Ferrante, Ph.D.
Project Manager, Sucraid

Through: Warren J. Prunella, AED, EC *WJP*
m p r
FROM : Marcia P. Robins, EC

SUBJECT: Economic Considerations: Petition for Exemption From
PPPA Requirements For Oral Prescription Drug **Sucraid**

The Directorate for Economic Analysis **reviewed** the economic, **small** business, and environmental effects of the subject proposal. Attached are the findings of these reviews.

Attachment(s)

**Economic Considerations: Petition For Exemption From PPPA
Requirements For Oral Prescription Drug
Sucraid**

The Consumer Product Safety Commission (CPSC) docketed a petition on August 6, 1997 from Orphan Medical Inc., a pharmaceutical manufacturer, requesting an exemption from the special or child-resistant (CR) packaging requirements of the Poison Prevention Packaging Act (PPPA) for the oral prescription (Rx) drug Sucraid (sacrosidase). The medication was designated an 'Orphan Drug' by the Food and Drug Administration (FDA). Drugs developed under the Orphan Drug designation have a small user population; incentives such as fast track approval and marketing exclusivity for seven years are offered by the FDA to companies that develop such drugs.

There are provisions under the PPPA for exempting drugs. Exemptions from CR packaging requirements have been granted for a variety of Rx drugs including sublingual dosage forms of nitroglycerin, anhydrous cholestyramine in powder form, all unit dose forms of potassium supplements, sodium fluoride drug preparations, and betamethasone tablets packaged in manufacturers' dispenser packages.

This report presents economic information on Sucraid provided by the manufacturer.

Product Use

Sucraid is an oral solution containing a yeast-derived enzyme. It is the first drug to be developed for use in the treatment of congenital sucrase-isomaltase deficient (CSID) patients who are missing the endogenous digestive enzyme. CSID is a chronic malabsorption disease in which patients are unable to metabolize and absorb sucrose, which leads to malnutrition.

The recommended dosage of Sucraid is 1-2 mL (22 to 44 drops), determined by the weight of the patient, taken with each meal or snack and diluted with water, milk, or infant formula. Patients are instructed to store the preparation in the refrigerator and discard the bottle 4 weeks after first opening due to the potential for bacterial growth.

Product Packaging

Sucraid is packaged in non child-resistant (CR) 118 mL plastic blow-molded, filled and sealed bottles that are a **self-**contained container/closure system. The cap on the bottle has a small spike on the inside that is used to pierce the sealed bottle tip at the time of first use. A scoop for measuring the correct dosage is also provided. The bottles are packaged two per paperboard carton.

Sales

According to company-provided information, the drug has the potential to be used by an estimated 3,000 to 10,000 patients in the United States. To date, there have been no commercial sales of the drug because it has just received marketing approval from the FDA. The retail price of the product has not been set.

Small Business Considerations

Sucraid will be marketed by only one company, Orphan Medical, Inc., for a minimum of seven years under the Orphan Drug program. The company is a small business manufacturer based on employment and sales. The proposed exemption from PPPA requirements would allow the company to avoid costs associated with obtaining CR packaging. According to a company spokesperson, obtaining CR packaging for this product would involve additional costs of over \$500,000 to develop, test, and receive FDA approval for new packaging.

The staff concludes that this exemption proposal will not have any significant economic effect on a substantial number of small businesses or other small entities.

Environmental Considerations

Pursuant to the National Environmental Policy Act, and in accordance with the Council on Environmental Quality regulations and CPSC procedures for environmental review, the staff assessed the possible environmental effects associated with the proposed exemption from CR packaging requirements under the PPPA for Sucraid.

The Commission's regulations at 16 CFR Sec. 1021.5 (c) (3) state that rules exempting products from special packaging requirements under the PPPA normally have little or no potential for affecting the human environment: In this case, such an exemption **would** result in no changes to current packaging. Therefore, exempting these products from the requirements of the PPPA will have no effect on the human environment and no environmental assessment or impact statement is necessary.

TAB D

Draft 5/18/98

Billing Code 6355-01

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

Poison Prevention Packaging Requirements;

Proposed Exemption of Sucraid

AGENCY: Consumer Product Safety Commission.

ACTION: Proposed rule.

SUMMARY: The Commission is proposing to exempt from its **child-resistant** packaging requirements the oral prescription drug Sucraid. Sucraid is a new liquid formulation of sacrosidase, a yeast derived form of the **sucrase** enzyme, used for the treatment of congenital sucrase-isomaltase deficiency. The Commission proposes **this** exemption because human experience has shown no evidence of serious toxicity.

DATES: Comments on the proposal should be submitted no later than _____ [insert date that is 75 days after publication in the FEDERAL REGISTER].

ADDRESSES: Comments should be mailed to the Office of the Secretary, Consumer Product Safety Commission, Washington, D.C. 20207, or delivered to the Office of the Secretary, Consumer Product Safety Commission, Room 502, 4330 East-West Highway, Bethesda, Maryland 20814-4408, telephone (301) 504-0800.

Comments may also be filed by telefacsimile to (301) 504-0127 or by **email** to cpsc-os@cpsc.gov.

FOR FURTHER INFORMATION CONTACT: Jacqueline Ferrante, Ph.D.,

Division of Health Sciences, Directorate for Epidemiology and Health Sciences, Consumer Product Safety Commission, Washington, D.C. 20207; telephone (301) 504-0477 ext. 1199.

SUPPLEMENTARY INFORMATION:

A. Background

The Poison Prevention Packaging Act of 1970 ("PPPA"), 15 U.S.C. 1471-1476, provides the Commission with authority to establish standards for the "special packaging" of household substances, such as drugs, when child resistant packaging is necessary to protect children from serious personal injury or illness due to the substance and the special packaging is technically feasible, practicable, and appropriate for such substance. Accordingly, the Commission requires that oral prescription drugs be in child resistant ("CR") packaging. 16 CFR 1700.14 (a) (10).

The Commission's regulations allow companies to petition the Commission for exemption from CR requirements. 16 CFR Part 1702. Possible grounds for granting the exemption are that:

(a) The degree or nature of the hazard to children in the availability of the substance, by reason of its packaging, is such that special packaging is not required to protect children from serious personal injury or serious illness resulting from handling, using or ingesting the substance, or

(b) Special packaging is not technically feasible, practicable, or appropriate for the subject substance, or

(c) Special packaging is incompatible with the particular substance.

16 CFR 1702.17.

On **July** 10, 1997, Orphan Medical, Inc. ("**Orphan** Medical") petitioned the Commission to exempt its product, Sucraid, from the special packaging requirements for oral prescription drugs. The petitioner stated that the exemption is justified because of lack of toxicity and lack of adverse human experience with the drug. The petitioner also stated that CR packaging is not technically feasible, practicable and appropriate for Sucraid. Because, as explained below, the Commission concludes that Sucraid lacks sufficient toxicity to justify special packaging, the Commission did not consider the technical feasibility, practicability, and appropriateness of special packaging for Sucraid.

Sucraid is a liquid formulation of sacrosidase, a yeast derived **form** of the sucrase enzyme. It is used to treat patients with congenital sucrase-isomaltase deficiency ("**CSID**"). The petitioner estimates that there are approximately 3000 to 10,000 cases of **CSID** in the United States. **CSID** is a condition characterized by absent or low levels of sucrase and isomaltase, two enzymes in the small intestine. **Sucrase** breaks down sucrose (table sugar) so that it can be absorbed. Persons with **CSID** have such symptoms as diarrhea, abdominal pain, bloating, and gas. Patients with severe **CSID** may require hospitalization for diarrhea, dehydration, malnutrition, weakness and muscle wasting. Sacrosidase is an enzyme replacement therapy that reduces the symptoms of **CSID**.

B. Toxicity Data

Sacrosidase is derived from bakers yeast. It is Generally Recognized as Safe ("GRAS") for use in food by the Food and Drug Administration ("FDA") . 21 CFR 170.30. Sucraid contains about 1.5 milligrams per milliliter of the enzyme in a 50:50 solution of glycerol and water.

One bottle of Sucraid contains 150 mg of protein, 59 ml of water and 59 ml of glycerol. Similar to dietary proteins, the protein component of Sucraid is digested to amino acids which are used to make new protein and are not expected to cause toxicity. Glycerol is a sweet liquid used as a solvent, preservative, and moisturizer. FDA recognizes glycerol as GRAS for use as a food. 21 CFR 182.1320. It is also used as a drug, for example, to reduce intraocular and intracranial pressure. It also can be used as a laxative.

Possible adverse effects associated with glycerol include nausea, vomiting, headache, and dehydration. Less commonly reported effects include diarrhea, thirst, dizziness, and mental confusion. Some more serious effects have been reported with intravenous administration of glycerol and with certain high risk patients. However, the Hazardous Chemicals Desk Reference indicates that glycerol is only mildly toxic by ingestion. In addition, the Handbook of Common Poisonings in Children characterizes glycerol as a laxative, stating that "acute exposure to most laxatives produces nausea, vomiting, and diarrhea, which are usually mild and self-limiting."

The CPSC staff found three cases in the National Electronic Injury Surveillance System ("NEISS") of children under five years old ingesting products containing glycerol. The products involved were a glycerol suppository, a baby enema preparation, and an ear solution. In all three cases the child was treated and released or examined and released without treatment. .

Thus, based on the information discussed above, the glycerol component of Sucraid is not likely to cause significant toxicity to children.

C. Human Experience Data

According to the petitioner, there have been three clinical trials of Sucraid, two of which are complete. The clinical investigators conducting the trials did not rate any of the adverse effects encountered as probably or definitely related to the drug. Some effects were considered to be possibly related to the drug.

The investigators considered most of the adverse effects to be unrelated to Sucraid and due to illnesses common to children (e.g., flu, ear infection and strep throat). Unrelated effects included sore throat, fever, cough, runny nose, diarrhea, cramping and abdominal pain.

The clinical investigator did rate some adverse events in the second trial as possibly related to Sucraid. These symptoms included abdominal pain, diarrhea, nausea, vomiting, constipation, dehydration, cramps, headache, insomnia, nervousness, and wheezing. The petitioner noted that many of

these were gastrointestinal symptoms typical of CSID. Thus, the dose of Sucraid given may not have been adequate to alleviate all symptoms of the disease. An asthmatic child had an acute hypersensitivity reaction (wheezing) to Sucraid that resolved without sequelae. This patient was withdrawn from the trial.

D. Action on the Petition

After considering the information provided by the petitioner and other available toxicity and human experience data, the Commission preliminarily concludes that the degree and nature of the hazard to children presented by the availability of Sucraid do not require special packaging to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting the substance. Therefore, the Commission voted to grant the petition and begin a rulemaking proceeding to exempt Sucraid from the special packaging requirements for oral prescription drugs.

E. Regulatory Flexibility Act Certification

Under the Regulatory Flexibility Act, 5 U.S.C. 601 et seq., an agency that engages in rulemaking generally must prepare proposed and final regulatory flexibility analyses describing the impact of the rule on small businesses and other small entities. Section 605 of the Act provides that an agency is not required to prepare a regulatory flexibility **analysis** if the head of an agency certifies that the rule will not have a significant economic impact on a substantial number of small entities.

• • •

The Commission's Directorate for Economic Analysis prepared a preliminary assessment of the impact of a rule to exempt Sucraid from special packaging requirements. The staff reports that because of the small number of cases of CSID (3,000 to 10,000 in **the** U.S.), the market for **Sucraid** is expected to be small. The petitioner, Orphan Medical, is a small manufacturer based on its employment and sales. Orphan Medical has marketing exclusivity'for Sucraid for seven years. The exemption from special packaging requirements will allow the company to avoid costs associated with obtaining CR **packaging**.

Based on this assessment, the Commission preliminarily concludes that the proposed amendment exempting Sucraid from special packaging requirements would not have a significant impact on a substantial number of small businesses or other small entities.

F. Environmental Considerations

Pursuant to the National Environmental Policy Act, and in accordance with the Council on Environmental Quality regulations and CPSC procedures for environmental review, the Commission has assessed the possible environmental effects associated with the proposed PPPA amendment.

The Commission's regulations state that rules requiring special packaging for consumer products normally have little or no potential for affecting the human environment. 16 CFR **1021.5(c)(3)**. Nothing in this proposed rule alters that **expectation.(3)** Therefore, because the rule would have no

adverse effect on the environment, neither an environmental assessment nor an environmental impact **statement** is required.

I. Executive Orders

According to Executive Order 12988 (February 5, 1996), agencies must state in clear language **the** preemptive effect, if **any**, of **new** regulations.

The PPPA provides that, generally, when a special packaging standard **issued** under the PPPA is in effect, "no State or political subdivision thereof shall have any authority either to establish or continue in effect, with respect to such household substance, any standard for special packaging (and any exemption therefrom and requirement related thereto) which is not identical to the [PPPA] standard." 15 U.S.C. 1476(a). A State or local standard may be excepted from this preemptive effect if (1) the State or local standard provides a higher degree of protection from the risk of injury or illness than the PPPA standard; and (2) the State or political subdivision applies to the Commission for an exemption from the **PPPA's** preemption clause and the Commission grants the exemption **through** a process specified at 16 CFR Part 1061. 15 U.S.C. 1476(c)(1). In addition, the Federal government, or a State or local government, may establish and continue in effect a non-identical special packaging requirement that provides a higher degree of protection than the PPPA requirement for a household substance for the Federal, State or local government's own use. 15 U.S.C. 1476(b).

Thus, with the exceptions noted above, the proposed rule exempting Sucraid from special packaging requirements would preempt non-identical state or local special packaging standards for the substance.

In accordance with Executive Order 12612 (October 26, 1987), the Commission certifies that the proposed rule does not have sufficient implications for federalism to warrant a Federalism Assessment.

List of Subjects in 16 CFR Part 1700

Consumer protection, Drugs, Infants and children, Packaging and containers, Poison prevention, Toxic substances.

For the reasons given above, the Commission proposes to amend 16 CFR part 1700 as follows:

PART 1700--[AMENDED]

1. The authority citation for part 1700 continues to read as follows:

Authority: Pub. L. 91-601, secs. 1-9, 84 Stat. 1670-74, 15 U.S.C. 1471-76. Secs 1700.1 and 1700.14 also issued under Pub. L. 92-573, sec. 30(a), 88 Stat. 1231. 15 U.S.C. 2079(a).

2. Section 1700.14 is amended by adding new paragraph (a) (10) (xx) to read as follows (although unchanged, the introductory texts of paragraph (a) and paragraph (10) are included below for context):

§ 1700.14 Substances requiring special packaging.

(a) Substances. The Commission has determined that the degree or nature of the hazard to children in the availability of the following substances, by reason of their packaging, is such that special packaging meeting the requirements of § 1700.20(a) is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substances, and the special packaging herein required is technically feasible, practicable, and appropriate for these substances:

* * * * *

(10) **Prescription Drugs.** Any drug for human use that is in a dosage form intended for oral administration and that is required by Federal law to be dispensed only by or upon an oral or written prescription of a practitioner licensed by law to administer such drug shall be packaged in accordance with the provisions of § 1700.15(a), (b), and (c), except for the following:

* * * * *

(xx) Sacrosidase (**sucrase**) preparations in a solution of . glycerol and water.

Dated: _____

Sadye E. DUM,

Secretary, Consumer Product Safety Commission

List of Relevant Documents

1. Briefing memorandum from Jaqueline Ferrante, Ph.D., EH, to the Commission, "Petition (PP 97-1) to Exempt Sucraid from the Special Packaging Requirements for Oral Prescription Drugs," _____, 1.998.

2. Memorandum from Jaqueline Ferrante, Ph.D., EH, to Mary Ann Danello, Ph.D., Associate Executive Director, EH, "Sucraid Review" April 1, 1998.

3. Memorandum from Marcia P. Robins, EC, to Jacqueline Ferrante, Ph.D., EH, "Economic Considerations: Petition for Exemption from PPPA Requirements for Oral Prescription Drug Sucraid," April 2, 1998.